UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/552,061	10/04/2005	Tsuyoshi Morishita	00005.001277	3919

5514 7590 08/09/2007

FITZPATRICK CELLA HARPER & SCINTO
30 ROCKEFELLER PLAZA
NEW YORK, NY 10112

EXAMINER	
WANG, CHANG YU	
ART UNIT	**PAPER NUMBER**
1649	
MAIL DATE	**DELIVERY MODE**
08/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/552,061	MORISHITA ET AL.	
	Examiner	Art Unit	
	Chang-Yu Wang	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-19 and 42-52* is/are pending in the application.

4a) Of the above claim(s) *6-19 and 42-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4 and 5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *4-19 and 42-52* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/1/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RESPONSE TO AMENDMENT

Status of Application/Amendments/claims

1. Applicant's amendment filed Jun 1, 2007 is acknowledged. Claims 1-3 and 20-41 are cancelled. Claims 4-19, and newly added claims 42-52 are pending in this application.

2. Newly submitted claims 42-52 and amended claims 6-19 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: amended claims 6-19 and new claims 42-52 encompass methods of using structurally different inhibitors, which are patentably distinct. For example, the claims directed to inhibitors examined in the first office action of the merits were lithium and SB-216763, which are very different from those with formula (I), (Ia), (IIa), (IIIa), (II), (III), (IIIb), (IV), (V) and are also very different from those of using antisense SEQ ID NOs: 15-17. Therefore, these claims are directed to different groups based on inhibitors with structures. In addition, many different species are contained within each group under each formula. There would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

(d) the prior art applicable to one invention would not likely be applicable to another invention;

(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Thus, search for all of the different groups and species would be a serious burden for the examiner.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 6-19 and 42-54 are withdrawn from consideration as being directed to a non-elected invention, there being no allowable generic or linking claim. See 37 CFR 1.142(b) and MPEP § 821.03.

3. Claims 4 and 5 are under examination in light of SB-216763 and lithium in this office action.

4. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response.

5. Applicant's arguments filed on Jun 1, 2007 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Objections

6. Claim 4 and 5 are objected to because of the following informalities: "neogenesis" is misspelled. The examiner interprets "neogenesis" as "neurogenesis". Appropriate correction is required.

Claim Rejections/Objections Withdrawn

7. The rejections to claim 38 under 35 U.S.C. 112-1st, 102(b), 103(a) are withdrawn due to the cancellation of the claim.

The rejection of claim 38 under 35 U.S.C. 112, second paragraph, for being indefinite because of the recitations of "substance" and "activity" and lack of antecedent bases is withdrawn in response to Applicants' cancellation of claim 38 and Applicants' amendment to the claims by reciting "allow neurogenesis" and specific substances.

Claim Rejections/Objections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 5 is rejected under 35 U.S.C. 112, first paragraph, while being enabling for enhancing neurogenesis of Tuj1 positive neurons or reversing the suppression effect of Aβ on neurogenesis by lithium chloride and SB-216763 to inhibit the expression of GSK-3β, does not reasonably provide enablement for a method of manufacturing Tuj1

positive neurons by inhibiting GSK3 to allow neurogenesis with all bisindolylmaleimide derivatives or pharmacological acceptable salts thereof as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims, for the reasons made of record for canceled claim 38 in Paper NO. 20070108 and as follows.

Applicants argue that amended claim 5 is enabled (p. 26 of the response). Applicants' argument has been fully considered but it is not persuasive.

In contrast to Applicants' assertion on p. 26 of the response, the specification fails to teach how to make and use of all bisindolylmaleimide derivatives that can be used in the claimed method. Based on the specification and prior art, Applicants are enabled for manufacturing neurons with anti-Tuj1 positive from neural stem cells by lithium chloride and SB-216763. However, the claims are not limited to the agents as set forth above. Applicants are not enabled for all bisindolylmaleimide derivatives to enhance neurogenesis since the specification fails to provide sufficient guidance as to enable one of skill in the art to practice the full scope of the invention. Although the specification describes several possible formula and possible modifications, Applicants fail to teach how to make and use these different possible bisindolylmaleimide derivatives. Thus, it is unpredictable whether other bisindolylmaleimide derivatives can be used to induce neurogenesis. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity is

unpredictable and the experimentation left to those skilled in the art is extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986). Thus, the skilled artisan cannot readily make and use the claimed invention as currently claimed without further undue experimentation. Accordingly, the rejection of claim 5 under 35 U.S.C. 112, first paragraph, because the specification does not enable the invention commensurate in scope with the claims is maintained.

9. Claim 5 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons made of record for canceled claim 38 in Paper NO. 20070108 and as follows.

Applicants argue that amended claim 5 is enabled in its full scope (p. 26 of the response). Applicants' argument has been fully considered but it is not persuasive.

In contrast to Applicants' assertion on p.26 of the response, the specification fails to demonstrate possession of all bisindolylmaleimide derivatives that can be used in the claim. Although the specification describes several possible formula and possible modifications, Applicants fail to demonstrate that Applicants are in possession of these different possible bisindolylmaleimide derivatives that can be used in the claimed method.

"An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the

chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004)"
Thus, the rejection of claim 5 under 35 U.S.C. 112, first paragraph, for failing to comply with the written description requirement is maintained.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 5 is rejected under 35 U.S.C. 102(b) as being anticipated by Ohkawa et al. (WO03/004485 (is also EP1411052), PCT/JP02/06776, published on Jan 16, 2003, filed on Apr 4, 2002 as evidenced by Ohkawa et al. (US 2004/0167171, published on Aug 26, 2004, which is a 371 of WO03/004485, currently issued as US Patent No. 7208495 on Apr 24, 2007), for the reasons made of record for canceled claim 38 in Paper NO. 20070108 and as follows.

Applicants argue that the reference of Ohkawa et al. (WO03/004485) is not available under 102 (b) because it was not published until Jan 6, 2003 (p.27 of the response). Applicants also argue that Ohkawa (WO'485) is not entitled to its PCT filing date (Apr 7, 2002) because it was not published in English (p. 27 of the response). Applicants argue that Ohkawa (WO'485 or US'171) does not teach compounds inhibiting GSK-3β and does not teach promoting neurogenesis because the compounds disclosed in Ohkawa (WO'485 or US'171) are different from the compounds recited in

the instant claims (p. 28 of the response). Applicants' arguments have been fully considered but they are not persuasive.

In response to Applicants' arguments on p. 27 of the response, Applicants' arguments are simply incorrect.

Based on MPEP, "(C) If the application claims foreign priority under 35 U.S.C. 119(a)-(d) or 365(a)>or (b)<, the effective filing date is the filing date of the U.S. application, unless situation (A) or (B) as set forth above applies. The filing date of the foreign priority document is not the effective filing date, although the filing date of the foreign priority document may be used to overcome certain references. See MPEP § 706.02(b) and § 2136.05."

The effective filing of the instant application is based on its filing date of the US application, which is its international filing date Apr 16, 2004. Ohkawa (WO'485) is published on Jan 6, 2003, which is qualified as a 102 (b) art, regardless of whether it was published in English since the publication date of Ohkawa (WO'485) is more than one year prior to the effective filing of the instant application. In addition, Ohkawa (WO'485) was published in English and designated in US so it is also entitled to its 102 (e) date Apr 7, 2002.

In addition, in contrast to Applicants' assertion on p. 28 of the response, Ohkawa (WO'485 or US'171) teaches a method of enhancing neurogenesis in neural stem cell cultures in the presence of a substance that inhibits the activity of GSK-3 (i.e as it relates to claim 5; see p. 153). Although Ohkawa (WO'485 or US'171) does not explicitly teach SB-216763 as an inhibitor of GSK-3, Ohkawa (WO'485 or US'171) does teach SB-216763 as an inhibitor of GSK (see p. 42, 1st col, line 39; p. 159 claims 49-66), which is also an inhibitor of GSK-3 as evidenced by Cross et al. (J. Neurochem. 2001. 77:94-102 cited in the previous office action). In addition, Ohkawa (WO'485 or

US'171) teaches a method of enhancing neuronal differentiation from cells isolated from 2-day old rat cerebral cortex (containing neural stem/progenitor cells) in a culture medium containing an inhibitor of GSK-3 including SB-216763 as described in the instant specification (i.e. a bisindolylmaleimide derivative, as it relates to claim 5; see p.153, [1252]-[1259]). The differentiated neurons were detected by an anti-β-III tubulin antibody, which is the same as the one used in the instant specification and is Tuj1 (i.e. as it relates to claim 5; see p. 153, [1255]-[1256]). Thus, claim 5 is anticipated by Ohkawa (WO'485 or US'171).

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 4 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johe (US Patent No. 6040180, issued on Mar 21, 2000) in view of Chen et al. (J.

Neurochem. 2000. 75: 1729-1734 as in IDS) and Cross et al. (J. Neurochem. 2001. 77:94-102 as in IDS), for the reasons made of record for canceled claim 38 in Paper NO. 20070108 and as follows.

Applicants argue that Chen and Cross do not teach neurogenesis because BrdU is a marker for DNA synthesis not for neurogenesis and Cross only teaches SB-415286 and SB-21673 as inhibitors of GSK-3 to protect neuronal cell death (p. 28-29 of the response). Applicants' arguments have been fully considered but they are not persuasive.

In contrast to Applicants' assertion on p. 28-29 of the response, the applied references do teach a method of manufacturing Tuj1 positive neurons in the presence of a GSK-3 inhibitor, such as lithium, SB-415286 and SB-216763.

In response to Applicants' argument with respect to BrdU, it is noted that neurogenesis in hippocampus induced by lithium as disclosed by Chen was detected with a combination of BrdU labeling and staining of a neuronal specific marker such as NeuN, which indicate neurogenesis is increased in hippocampus in the presence of lithium stimulation.

In response to Applicants' argument with respect to SB-415286 and SB-21673 are inhibitors of GSK-3 to protect neuronal cell death instead of enhancing neurogenesis, it is noted that although Cross does not explicitly teach neurogenesis by GSK-3 inhibitors (SB-415286 and SB-216763), neurogenesis by GSK-3 inhibitors (SB-415286 and SB-216763) would be an intrinsic result of administration of GSK-3

inhibitors in cultured neurons of the PNS and CNS because the procedures and materials disclosed in Cross are the same as in the instant claims.

In this case, Johe (US'180) teaches a method of generation of neurons from neural stem cells that are isolated from either embryonic or adult brains by stimulating these neural stem cells with a growth factor such as BDNF (i.e. as it relates to claims 4 and 5; see col. 15-18, lines 14-62; col. 35-36, claims 1-6). Although Johe (US'180) does not teach use of GSK-3 inhibitors, Chen et al. teach that lithium can enhance neurogenesis in the adult hippocampus (see p. 1729, abstract) and lithium as an inhibitor of GSK-3β is evidenced by Eldar-Finkelman (see p. 130, 2nd col. 2nd paragraph. Trends in Mol. Med. 2002. 8:126-132 cited in the previous office action). Cross et al. also teach several small-molecule inhibitors of GSK-3, SB-415286 and SB-216763 can enhance neuronal survival and protect neuronal cells from cell death in primary neuronal cultures of the peripheral nervous system and the central nervous system (see p. 94, abstract), which would intrinsically enhance neurogenesis since the procedures and materials disclosed in Cross are the same as in the instant claims. Thus, the teachings of Chen et al. and Cross et al. provide a motivation and expectation of success in substituting growth factors with inhibitors of GSK-3β such as lithium, SB-415286 and SB-216763 to culturing and generating neurons with Tuj1 positive.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to use an inhibitor of GSK-3β, such as lithium and SB-216763 to enhance neurogenesis of Tuj1 positive neurons from neural stem cells since lithium has been shown to induce neurogenesis in the hippocampus and SB-216763

and lithium are inhibitors of GSK-3β. Thus, one of ordinary skill in the art would have motivated and would have expected success in generating neurons by incubating neural stem cells with an inhibitor of GSK-3β such as lithium or SB-216763 to enhance neurogenesis. Accordingly, the rejection of claims 4 and 5 under 35 U.S.C. 103(a) for being unpatentable over Johe (US Patent No. 6040180) in view of Chen et al. and Cross et al. is maintained.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4 and 5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4 and 5 recite the limitations "the activity" in line 5. There is insufficient antecedent basis for this limitation in the claims.

Conclusion

NO CLAIM IS ALLOWED.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Thursday and every other Friday from 8:30 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at (571) 272-0841.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/CYW/
Chang-Yu Wang, Ph.D.
July 18, 2007

ROBERT C. HAYES, PH.D.
PRIMARY EXAMINER